Chiral Atropisomeric Indenocorannulene Bowls: Critique of the Cahn-Ingold-Prelog Conception of Molecular Chirality

Wang, Yujia ; Allemann, Oliver ; Balaban, T Silviu ; Vanthuyne, Nicolas ; Linden, Anthony ; Baldridge, Kim K ; Siegel, Jay S

Abstract: Chiral corannulenes abound, but suffer generally from configurational lability associated with bowl-to-bowl inversion,[1] thus obviating questions of stereogenicity and stereoelement construction.[2] In contrast, peri-annulated corannulenes show greatly increased barriers for bowl-to-bowl inversion; specifically indenocorannulenes invert on a time scale too slow to observe by normal NMR methods and raise the possibility of creating chiral atropisomeric bowl-shaped aromatics.[3] Two methods for preparing indenocorannulene from simple 2-haloarylcorannulenes—silyl cation C–F activation,[4] and Pd-mediated C–Cl activation[5]—enable the synthesis of an array of such chiral atropisomeric indenocorannulenes.[6] Resolution of the enantiomers by high-performance liquid chromatography over chiral support phases motivates the study of chiroptical properties, the assignment of absolute "Cartesian" configuration, and the assessment of configurational stability.[7] These studies bring into question any systematic assignment of nontrivial stereoelements (i.e. not the molecule in its entirety) and refute any assertion of congruence between "Cahn–Ingold–Prelog elements" and the physical or "Cartesian" basis of chirality

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Chiral Atropisomeric Indenocorannulene Bowls: Critique of Cahn-Ingold-Prelog Theory of Chirality?

Yujia Wang, Oliver Allemann, T. Silviu Balaban, Nicolas Vanthuyne, Anthony Linden, Kim K. Baldridge, Jay S. Siegel**

((Dedication----In memory of our dear colleague Silviu.))

Chiral corannulenes abound, but suffer generally from configurational lability associated with bowl-to-bowl inversion, [1] thus obviating questions of stereogenicity and stereoelement construction,[2] In contrast, peri-annulated corannulenes show greatly increased barriers for bowl-to-bowl inversion, specifically indenocorannulenes invert on a time scale too slow to observe by normal NMR methods and raise the possibility of creating chiral atropisomeric bowl-shaped aromatics.[3] Two methods for preparing indenocorannulene from simple 2-haloarylcorannulenes – Silyl cation C-F activation,[4] and Pd mediated C-Cl activation[5]– enable the synthesis of an array of such chiral atropisomeric indeno-corannulenes.[6] Resolution of the enantiomers by high performance liquid chromatography over chiral support phases motivates the study of chiroptical properties, the assignment of absolute "Cartesian" configuration and assessment of configurational stability. [7] These studies bring into question any systematic assignment of non-trivial stereoelements (i.e. not the molecule in its entirety) and refute any assertion of congruence between "Cahn-Ingold-Prelog elements" and the physical or "Cartesian" basis of chirality.

The minimum energy static bowl form of indenocorannulene manifests bilateral (Cs) symmetry. All of the hydrogen atoms are chirotopic (local symmetry C_1) and therefore substitution of any single hydrogen by a non-hydrogen atom lowers the symmetry of the molecule to C_1. This study focuses on chiral molecules resulting from substitutions to the indeno-6-membered ring.

Iodocorannulene couples efficiently with a variety of 2-haloarylboronic acids to provide the immediate synthetic precursors to indenocorannulenes **1a-1f** (Scheme 1). Fluoro precursors were subjected to silyl cation C-F activation/coupling, whereas chloro precursors underwent Pd catalyzed C-Cl activation/coupling. Although both methods cleanly provide product, the yields for Pd catalyzed C-Cl activation/coupling are in general higher (80 % vs 40 %, see supporting information) and reaction conditions are less sensitive to moisture and oxygen.

[*] Y. Wang, Prof. Dr. K. K. Baldridge, Prof. Dr. J. S. Siegel Health Sciences Platform, Tianjin University 92 Weijin Road, Nankai District, Tianjin-300072 (China) E-mail: dean_spst@tju.edu.cn

Prof. T. Silviu Balaban, Prof. Nicolas Vanthuyne Dept. of Chemistry, Marsailles, France

Prof. Dr. Anthony Linden, Dept. of Chemistry, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland

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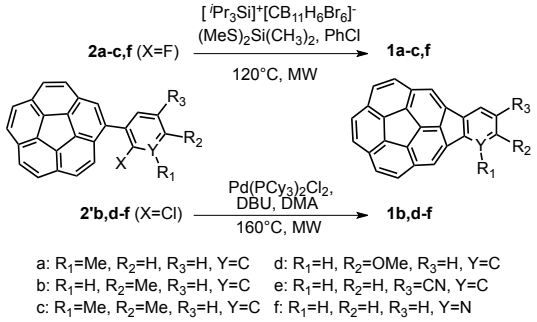
Indenocorannulenes in general embody useful photophysical and electrochemical properties. Compared to corannulene with a first reduction potential of -2.49 V, the parent monoindeno corannulene has a first reduction potential of -2.06 V and azaindenocorannulene **1f** has a first reduction potential of -2.00 V. [8] Clearly the influence of introducing an indeno annulation (ca. 0.5 V) outweighs the modulating influence of simple substituents (<0.1 V). Across the series, the optical spectra display absorption peaks around 270 nm and 300-350 nm, and one broad emission peak at about 580 nm (ca. 100 nm width at half-height). Quantum efficiencies are routinely observed to be less than 1%.



Scheme 1. Chiral indenocorannulenes by C-F or C-Cl activation.

Indenocorannulenes are predicted to have high barriers and low rates for bowl-inversion.[3] As such, one expects the products of the reactions described above, monosubstituted derivatives **1a-1f,** to be non-fluxional racemic mixtures. HPLC over chiral stationary phase effected the resolution of **1a-1f**, specifically using (S,S)-WHELK-O1, Chirapak ID, (S,S)-WHELK-O1, Chirapak IE, Chirapak IG, and Chirapak IC, respectively (see supporting information).

Kinetic studies on the first order decay of optical activity allowed determination of activation free energies for racemization by bowl-to-bowl inversion (Table 1). The kinetics of enantiomerization were measured in ethanol at 78°C. Rate constants of enantiomerization were determined assuming first-order decay of the optical activity at early stages of the reaction. Half-lives of racemization were determined using the first-order rate constants.

B97-D/Def2-TZVPP(ethanol)//B97-D/Def2-TZVPP bowl ground state and flat transition state geometries enabled the prediction of the energetics of the bowl-flipping model for comparison to experimental free energies of racemization ($\Delta G^{\neq}$). Predicted $\Delta G^{\neq}$ for **1a-1f** agree well with experimental (RMS deviation < 1 kJ/mol) and follow the same trend as experiment. All data indicate that the enantiomers of **1a-1f** are configurationally stable on the order of several hours at 60 °C (days at RT in solution)

Cyano derivative **1e** displays the largest activation energy and longest half-life, whereas dimethyl derivative **1c** has the smallest

activation energy possibly due to the repulsive interactions between hydrogens of the adjacent methyl groups and the neighboring hydrogen of the corannulene rim. The lower barrier of 1-methyl (**1a**) vs 2-methyl (**1b**) supports this supposition. Albeit a rather small influence, the other three compounds also have low bay region congestion and all display higher barriers. This trend is a local correlation among close cognates that does not hold generally; for example, bowls with flanking helicene character will no doubt display higher barriers to enantiomerization.[9]

Table 1. Experimental and Theoretical Barriers to Racemization (78° C, ethanol).

Compound	k (10^5/sec)	$\Delta G^{\neq}$ (kJ/mol)	[calcd][1]	$T^{1/2}$ (hrs)
1a	3.31	116.6	[115.1]	2.90
1b	2.09	117.9	[117.0]	4.60
1c	3.90	116.1	[113.4]	2.47
1d	1.89	118.2	[117.2]	5.09
1e	1.14	119.7	[119.1]	8.41
1f	1.17	118.5	[117.6]	5.60

[1]B97D/Def2-TZVPP(ethanol)//B97D/Def2-TZVPP

In principle, solvent polarity could influence the activation parameters of the bowl inversion process by stabilization of the bowl state relative to the flat state. For corannulene the bowl state has a dipole moment along the 5-fold symmetry axis and the flat state has a dipole moment of zero, based on D_5h symmetry; for indenocorannulene these symmetry restrictions are released but the dipole moment in the bowl form is still substantial (2.74 D) and oriented nearly normal to the bowl-hub plane, whereas in the flat form the dipole moment is small (0.27 D) and is oriented in the plane. In an attempt to address the role of the bowl-dipole, the racemization process for **1a** was investigated at three temperatures in ethanol, in chloroform and in cyclohexane. The computations predict a dipole moment of 2.80 D for the bowl state of **1a** roughly "normal" to the best plane of the bowl hub atoms and a 0.61 D in the plane of the flat form. Although experimental activation free energies could be determined with reasonable precision (±1.0 kJ/mol), the precision of activation enthalpy and entropy is insufficient to establish a causal difference in the barriers to racemization of **1a** as a function of solvent. Computational data on the activation enthalpy as a function of support the classical idea that more polar solvents should lead to higher barriers by stabilization of the more polar bowl state; but only by a very small amount, ca. 2 kJ/mol across the series ethanol, hexane, gas phase. (For complete details see supporting information).

Crystals of enantiomerically pure **1d,** suitable for X-ray diffraction analysis, were obtained from CH_2Cl_2 / hexane (Figure 1).[10] Two symmetry-independent molecules with highly similar conformations occupy the asymmetric unit (r.m.s. deviation of the atoms of the two molecules is 0.029 Å). Crystal packing ($P2_1$) reveals polar columns of molecules stacked bowl-in-bowl (Figure 1). The experimentally determined bowl depth of **1d** is 1.068 Å. On the basis of the correlation of bowl depth to inversion barrier, a bowl depth of around 1.07 Å should correlate with a barrier of around 120 kJ/mol,[3] in good agreement with the present experimental findings. The polar unit cell is consistent with the packing of a chiral enantiopure molecule. Nonetheless, enantiopure crystals of **1d** did not allow an unambiguous determination of the absolute configuration (Parson's parameter, [11] $z = 0.19(11)$). The best guess configuration is displayed in Figure 1, notwithstanding unforeseen racemization or crystal habit issues.

Vibrational circular dichroism (VCD) offers an alternative way to establish absolute configuration by comparison of experimental and computational spectra. [12] The VCD of **1a-1f** were measured ($CHBr_3$) and compared to B97-D/Def2-TZVPP ($CHBr_3$) determined spectra. Comparison of the regions of the spectra unperturbed by solvent peaks, 800-1000 cm^{-1} and 1250-1600 cm^{-1}, allowed configurational assignment for all enantiomers (Figure 2), which in the case of **1d**, corroborates the crystallographic absolute structure supposition.

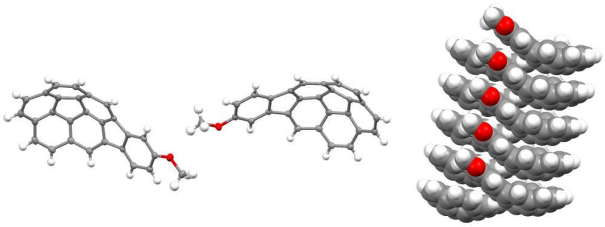


Figure 1. The asymmetric unit (left) and crystal packing (right) in the crystal structure of **1d**.

Electronic circular dichroism (ECD) can also provide an enantiomeric spectroscopic signature;[13] however, with fewer transitions it can be less robust than VCD. In light of the assignment by VCD, one can use ECD as an independent confirmatory determination. In the present series, comparison of experimental and TD-CAMB3LYP[10e]/Def2-TZVPP(ACN)//B97-D/Def2-TZVPP determined ECD for **1a-1f**, arrives at the same configurational assignment as that obtained with VCD.

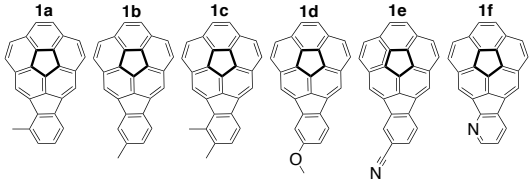
Although identifying whether a geometric molecular model is chiral is evident by its symmetry, establishing the enantiomeric character of the represented physical compound relies on the observation of various chiropical properties such as those described above.[14] Neither the symmetry of the model nor observation of chiroptical properties requires a specification of molecular bonding. As such, linking stereoisomerism to a valence-bond model inherently erodes the model's claim to being the basis for molecular chirality.

Enantiomers are the one class of stereoisomers that are required by symmetry independent of bonding model, and one sees historically their configuration originally labelled with regard to physical properties, such as optical rotation (d/l) or the Cotton effect.[15] If experimental conditions are well defined, then the absolute configuration of a compound could be linked one-to-one with its properties; however, the general connection between name and configuration is limited. That is to say you can not easily draw the structure of specific absolute configuration directly from reading the chiroptical property. Strategies, such as octant rules or more sophisticated chirality functions, have attempted to link properties to configuration by general procedures.[16]

Since the time of van't Hoff, stereoisomers have been defined specifically with regard to permutations over molecular valence-bond frameworks, for example a tetrahedral stereocenter – van't Hoff's classically labelled "asymmetric center".[17] Fischer-Rosenoff conventions (D/L) moved the discussion of nomenclature closer to that of defining a configuration on the basis of the geometry of the model rather than one on the basis of the properties of the compound, but the reliance on valence bonds weakens it generality as regards chirality. [18]

Believing they had found an underlying set of elements of chirality, Cahn-Ingold-Prelog proposed their famous nomenclature of centers, axes and planes. [19] Unfortunately, they were unaware of

the fact that in the case of the regular tetrahedron, the symmetry group T_d overlaps one-to-one with the maximal permutation group S_4, leading some to mistake permutation operations as generally equivalent to symmetry operations.[2] Furthermore, they neglected Ruch's topological analysis on the limitations of the definability of homochiral taxonomies.[20] Thus, boldly, yet fatuously, they claimed that molecular chirality is reducible to causative "elements of chirality."



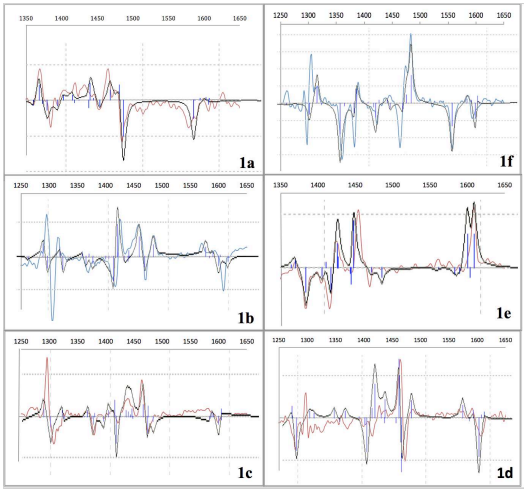


Figure 2. B97-D/Def2-TZVPP (gray) and Exptl (1st eluted red; 2nd eluted blue) VCD spectra of **1a-f** (Structure in header) from 1350 to 1650 cm^{-1} in $CHBr_3$.

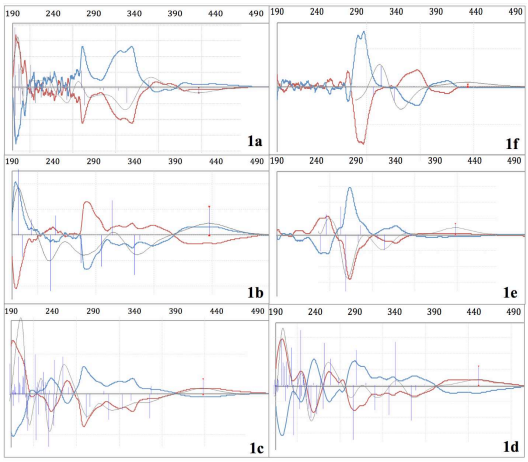


Figure 3. TD-CAMB3LYP/Def2-TZVPP(ACN)//B97-D/Def2-TZVPP (gray) and Exptl (1st eluted red; 2nd eluted blue) ECD spectra of **1a-f** from 190 to 490 nm in acetonitrile.

The importance of this historical discussion to the present article lies in the fact that the structures of **1a-1f** possess no tetrahedral atoms suitable for serving as a tetrahedral stereogenic element, and no suitable stereogenic elements within the center, axes, plane, paradigm, yet these are chiral molecules which have been prepared and resolved into enantiomeric forms. Thus, they are a fundamental contradiction to the Cahn-Ingold-Prelog basis for chiral factorization.

One could in principle arbitrarily define some set of 4 atoms specific to this class of structure, but this only underlines the contrived connection between geometric chirality and the commonly used chiral-element nomenclature popularized by Prelog and co-workers. There are a myriad of chiral materials to which application of Cahn-Ingold-Prelog rules and its notions are ill suited. Indeed, the nomenclatural rules applied to bowls, [21] fullerenes,[22] and a host of other systems amply exemplify that Cahn-Ingold-Prelog "elements of chirality" were never more than an ad hoc solution to the configurational labelling problem – neither elementary nor inherently chiral.

For indenocorannulene isomers **1a-f**, a simple labelling for archival purposes is desirable. To emphasize the distinctly non-Cahn-Ingold-Prelog nature of these names, the symbols 乒 and 乓 are appropriate for denoting the classes of enantiomers (Figure 4). Orienting the convex-facing indenocorannulene skeleton with its mirror plane vertical and the benzene ring at 6 o'clock, then substituents to the left are 乒 and to the right are 乓. [23]

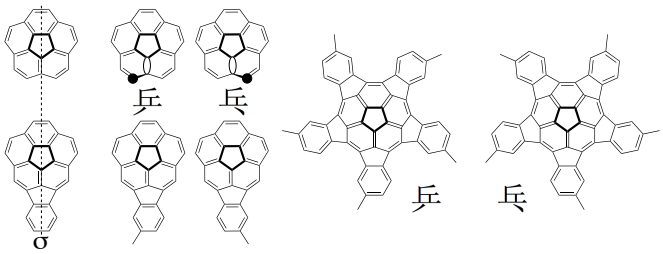


Figure 4. Configurational labels 乒 and 乓 for X-**1** and X_5-pentaindenocorannulene.

Although one can also use 乒乓 to label penta-substituted pentaindenocorannulenes, X_5-pentaindenocorannulene, it must be acknowledged that 乒乓 is a "whole-molecule" label and not simply ascribable to being five stereogenic elements of type X-**1**. Despite the structural parallel between X-**1** and its 5-fold symmetric analog X_5-pentaindenocorannulene, the five spoke axes do not qualify as independent stereogenic elements; permutation at any one spoke in X_5-pentaindenocorannulene does not yield a diastereomer but rather a constitutional isomer. Thus, 乒乓 can be used for compounds of type X-**1** and X_5-pentaindenocorannulene but further elaboration is needed before this can be generally applied to bowl-compounds.

Enantiomers **1a-1f** can also address the ill-conceived notion of quantification of chirality.[24] [25] Whereas phenomena arising from a specific chiral diastereomeric relationship can be quantified through a selected measurable, there is no assurance that another chiral diastereomeric relationship among the same set of compounds will give rise to the same order. In other words, the compound with the highest optical rotary power need not also show the largest separation factor on a chiral HPLC column.

To exemplify, consider a few phenomena upon which a ranking of "more chiral" could be made, but which bring home the contradiction inherent in such rankings: 1) configurational stability; 2) chiroptical power; 3) enantioselective recognition. For bowl-shaped enantiomers **1a-1f** configuration stability is limited by the bowl inversion barrier, which is also the barrier to enantiomerization. On the basis of this criterion, **1e**, with the highest barrier, would be the most chiral (cf. Table 1). Chiroptical power could be viewed as the largest absolute $[\alpha]_D$, in which case **1d** is most chiral, or the

largest ECD Δε, which would favor **1e**. Enantioselective recognition if gauged by degree of separation over a chiral chromatographic substrate could favor **1f**; but what substrate should be the reference? Ultimately, fanciful schemes devoted to quantification of chirality reveal more about the scientific biases of the proponents than the geometrical or physical nature of the structures in question. They are further obviated by the excellent job modern electronic structure theory does at predicting molecular properties including chiroptical properties, as can be seen from the comparison of experiment and theory above (cf. Tables 2 and 3).

Given our epistemological position that chirality in molecules is different than in molecular models, because molecular chirality requires observable anisochrany, we arrive at the issue of crypto-dissymmetry. [26] In a chiral molecule, all points are chirotopic and the local symmetry across any region is also chiral. Therefore, although the hydrogens straddling the 12-6 o'clock axis in indenocorannulene are symmetry equivalent and enantiotopic, those same positions in **1a-1f** are not. The symmetry non-equivalent diastereotopic hydrogens straddling 12 o'clock should manifest in the ^{1}H NMR spectrum as a doublet of doublets, rather than as a singlet, anticipated for enantiotopic hydrogens. When the chemical shift difference between the two sites approaches zero (in a practical sense, when it is less that the coupling constant) the spectrum becomes non-first order and manifests a pseudo-singlet, which masks the anisochrony. Examining **1a-1f** at 400 and 600 MHz, all except **1d** appears to manifest a singlet; however, closer examination shows tiny wing peaks at the coupling constant distance from the central peak revealing the cryptoclastic chiral character and allowing one to deduce the chemical shift difference. With this method, one sees the strongest effect for **1d**, followed by **1e** and **1f.** For **1a-1c** the effect is indiscernible at these field strengths. Quantum chemical computational methods predict the trend of these effects well.[27]

In conclusion, this new set of chiral bowl-shaped molecules opens an avenue to the study of chiral materials obviating the discussion of chiral elements. They underline the distinction between chirality and stereoisomerism pointed out three decades ago. Their general physical properties and propensity for shape-selective molecular recognition bodes well for the development of cognates capable of replacing classical chiral scaffolds.

Table 2. High-order effects for two-spin systems (400 and 600 MHz)

Cmpnd	$2\times i_2$[a]	$2\times i_1$[b]	$\nu_1 - \nu_4$[c]	$\nu_2 - \nu_3$[d]	Calcd[e]
1d	1.76	0.15	19.2	1.64	7.80
	2.00	0.08	21.6	0.86	5.20
1e	1.95	0.10	18.0	0.92	7.14
	1.80	0.06	18.0	0.60	4.76
1f	1.84	0.05	18.0	0.49	3.42
1b					2.34
1c					0.48
1a					0.48

[a] Integration of proton at the 12 o'clock position; [b] Integration of wing peak; [c] Coupling constant of wing peak; [d] coupling constant of proton at the 12 o'clock position; [e] CSGT B97-D//Def2-TZVPP (dichloromethane).

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